Amyloid heart disease

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The amyloidoses comprise a collection of disorders in which proteins, some native and some mutated, are deposited in tissues. These proteins self-assemble themselves to form an ordered fibrillar matrix termed amyloid. Currently, more than 20 different proteins have been identified, the most common with as many as 100 different mutations per protein. Despite these figures, the conditions that arise clinically are not that common. This undoubtedly results in a number of such individuals not being identified, or typically only when it is too late to effect a cure.

This article describes the features, diagnosis and treatments for the different types of amyloid that affect the heart.

Introduction

Several types of amyloidosis involve the heart (**table 1**), often with devastating consequences. In many cases prognosis is further worsened by systemic multi-organ involvement. For the primary care physician, two types are important to identify as they will often present with heart involvement. These include AL amyloid (previously termed primary) and some of the hereditary forms of amyloid.

The remaining forms either involve the heart rarely, as in secondary amyloid (AA) or rather late in life as in cases of senile systemic amyloid (SSA) and isolated atrial amyloid (IAA). Notwithstanding, these latter forms are still capable of causing significant mechanical dysfunction and rhythm disturbance.

Making a diagnosis

Many disorders can be confused with amyloid heart disease, most commonly forms of intrinsic hypertrophic cardiomyopathy (HCM), other deposition diseases and in some cases Fabry's disease.[1]

Cardiac involvement is usually first suspected from the appearances on echocardiography. The heart walls are usually globally thickened and characteristically this often includes the inter-atrial septum. The myocardium demonstrates an increased scintillation pattern (granular sparkling) although this is certainly not specific for amyloid. Valve leaflets and the pericardium may be thickened and there is often a modest pericardial effusion. While both atria will usually be dilated, the ventricular chambers are rarely dilated. Doppler interrogation of ventricular inflow will show the characteristic restrictive features of an infiltrative cardiomyopathy.

A low or normal voltage electrocardiogram (ECG) in the presence of apparent left ventricular 'hypertrophy' is very suggestive of heart involvement, as are Q-waves without prior history of myocardial infarction. Tissue Doppler techniques have proved helpful in distinguishing amyloid

Table 1. Types of amyloid, the monomer protein sub-units and the degree of cardiac involvement

Amyloid type	Amyloidogenic protein sub-units	Heart involvement
AL	Immunoglobulin light chains of kappa and lambda types	Frequent and severe
TTR	Mutant (and wild-type) transthyretin molecules	Severe with particular mutations (Leu55Pro, Val30Met, Val122Ile, Tyr78Phe)
Apo AI	Mutant apolipoprotein AI molecules	Severe heart involvement can occur
AFib	Mutant fibrinogen molecules	Severe heart involvement can occur
AGel	Gelsolin	Rare, but heart involvement can occur
IAA	Atrial natriuretic peptides	Severe heart involvement possible in the elderly
SSA	Wild-type (non-mutant) transthyretin	Severe heart involvement possible
AA	Amyloid protein A	Rare, but severe heart involvement can occur

Key: AA = reactive systemic amyloidosis; AFib = hereditary fibrinogen amyloidosis; Apo AI = hereditary apolipoprotein AI amyloidosis; SSA = senile systemic amyloidosis; TTR = transthyretin

from other causes of true hypertrophy and in characterising ventricular dysfunction.[2] Myocardial velocity profiles in patients with amyloid heart involvement show characteristics that differ from hypertrophied ventricular walls due to hypertension or HCM. Imaging amyloid heart disease using magnetic resonance imaging (MRI) with gadolinium enhancement, can also help differentiate amyloid from other causes of wall thickening, particularly HCM.[3]

Serum amyloid P scintigraphy scanning

The extent of amyloid deposition, of any type, can be assessed by serum amyloid P component (SAP) scintigraphy.[4] SAP is a normal plasma protein that binds reversibly to amyloid deposits of any type. While useful for imaging and quantifying amyloid in the liver, kidneys, spleen and bone marrow, it is not useful for identifying amyloid in the heart, due to the large blood pool and cardiac motion.

Histological and genetic diagnostic procedures

A formal histological diagnosis is made from either a screening biopsy, such as rectal or abdominal fat biopsy, or from an affected organ, for example kidney, liver or nerve. Amyloid deposits stain with Congo red and produce red–green birefringence when viewed under cross-polarised light. Cardiac biopsy may be indicated when there is no suggestion of extra-cardiac amyloid or when the diagnosis is uncertain. In AL amyloid, serum and or urine electrophoresis and immunofixation will detect a monoclonal immunoglobulin in 80–90% of cases. The availability of techniques to estimate free light chains has revolutionised the diagnosis and management of AL amyloid disease. In cases where there remains doubt about amyloid fibril type, DNA analysis to exclude hereditary amyloidosis and even amyloid fibril protein sequencing may be required. A bone marrow biopsy should be performed to quantify the plasma cell population, exclude myeloma and also to stain for amyloid, which if present is strongly suggestive of AL type.

AL amyloidosis

AL amyloidosis is the most commonly recognised form of amyloid in the UK. AL amyloid fibrils are derived from monoclonal immunoglobulin light chains produced by a plasma cell dyscrasia. While organ dysfunction is probably due, in the main, to the disruptive physical presence of amyloid deposits, there is good evidence that these light chains are inherently cytotoxic.[5,6]

AL amyloid presenting with heart failure has a very poor prognosis, with a median survival reported as low as four months.[7] In the absence of treatment, the natural history of AL amyloidosis is that of a progressive and fatal disease within two years in about 80% of patients.[8] The disease is usually renal or cardiac dominant in character with death an early outcome in the absence of treatment.[7,9] **Table 2** illustrates the typical clinical features found in AL amyloid disease. A low or normal voltage ECG (**figure 1**) in the presence of apparent left ventricular 'hypertrophy' on echo (**figure 2**) is very suggestive of AL heart involvement, as are Q-waves without prior history of myocardial infarction. Additional

Table 2. Clinical features characteristic of amyloid disease in general, their associated significance and notes

Clinical feature	Significance and notes
Macroglossia* (**figure 3**)	Change in voice or taste. Teeth indentation marks on lateral borders of tongue often seen
Skin thickening	Particularly of the 'muzzle' region of face*
Brittle nails	
Raccoon eyes* (**figure 4**)	Peri-orbital haemorrhages, may occur spontaneously
Petechiae, bruising and haemorrhage (**figure 5**)	May present with a gastrointestinal tract haemorrhage
Carpal tunnel syndrome	May occur several months or years earlier
Hepatomegaly	May be due to congestion and/or infiltration
Adrenal dysfunction	A further cause of hypotension
Thyroid dysfunction	A further cause of fatigue and oedema
Diarrhoea and malabsorption	Hypoalbuminaemia contributes to oedema
Neuropathies	More often a feature of non-AL types of amyloid
Proteinuria	Frequently in the nephrotic range
Hypotension	May be postural
Cachexia	From gastrointestinal tract involvement

*Classic stigmata of AL amyloid disease

Figure 1. A 12-lead electrocardiogram in a patient with extensive AL amyloid heart disease illustrating the very low voltage limb lead complexes and Q-waves in the anterior chest leads. Note that the patient remains in sinus rhythm despite the extent of involvement

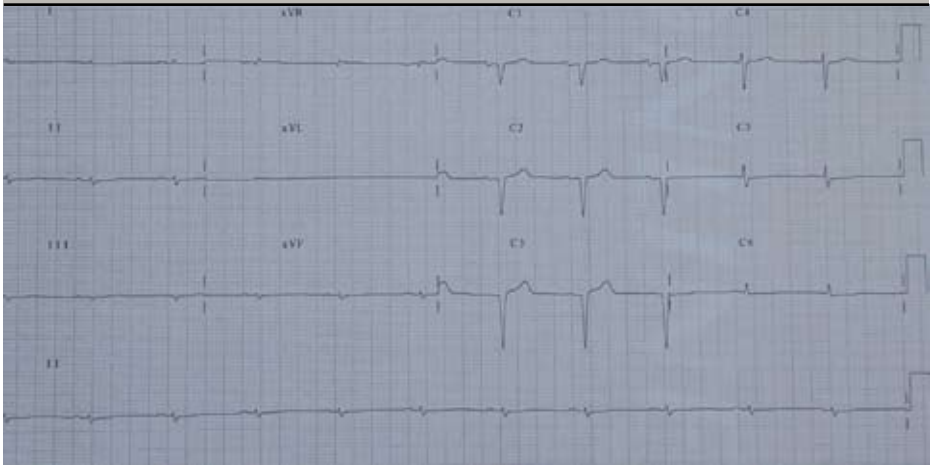
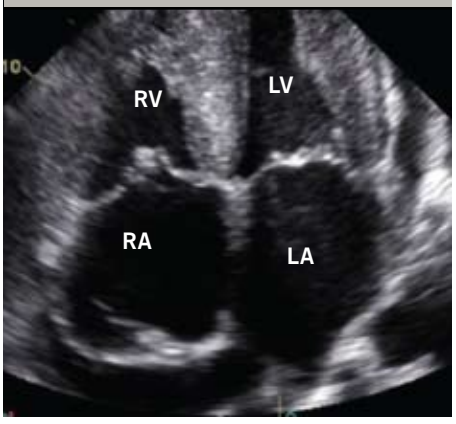


Figure 2. A four-chamber apical view echocardiogram showing, bi-atrial dilatation, valve thickening, thick ventricular walls, interventricular and inter-atrial septum. Note that the ventricular chambers are not dilated, an almost universal characteristic of amyloid heart disease



electrocardiographic and echo features of AL amyloid heart involvement are shown in **table 3** and **figure 2**.

Table 3. Clinical, electrocardiographic and echocardiographic features of cardiac involvement by AL amyloid

Cardiac feature	Notes
Right-sided heart failure	Raised JVP, oedema, third heart sound and hepatomegaly
Hypotension	May be postural. Syncope a very poor prognostic sign
Heart size may be normal (**figure 6**)	On a chest radiograph
Low voltage ECG	Mean limb lead voltage less than 0.5 mV
Apparent Q-waves on ECG	Usually anterior chest leads but may be inferior leads
Echo suggests LVH	Not true 'hypertrophy'
Thickened RV free wall on echo	Best seen on sub-costal views
Ventricles are rarely dilated	Aside from early dilatation of the right ventricle
Thickening of the inter-atrial septum	Best seen on sub-costal views
Granular appearance to myocardium	Not specific to amyloid heart disease
Valves appear thickened	Not usually that dysfunctional
Bi-atrial dilatation	Appear static, with an 'owl eye' appearance on echocardiogram apical four-chamber view
Thrombi may be seen in chambers	Thromboembolic events may be a presenting feature
Doppler will suggest restrictive pattern	Shown on interrogation of ventricular inflow
Pericardial and pleural effusions	May be due to heart failure and/or pericardial or pleural involvement

Key: ECG = electrocardiogram; JVP = jugular venous pressure; LVH = left ventricular hypertrophy; RV = right ventricular

Management of amyloid heart disease

Patients with AL (and non-AL) forms of cardiac involvement may benefit symptomatically from conventional heart failure therapies. Careful titration of diuretics remains the mainstay of management. Orthostatic hypotension may require support stockings and sometimes the use of fludrocortisone. The alpha agonist midodrine can be very effective as a pressor agent. Calcium channel blockers and beta blockers should be used with caution due to their negative inotropic effects. Reports suggest digoxin can bind to amyloid fibrils with increased toxicity, but judicious low-dose treatment can sometimes be beneficial. Permanent pacing, resynchronisation pacing and automatic implantable cardioverter defibrillator (AICD) implantation may prove useful in a small proportion of cases.

Specific management of AL amyloid

Treatment of AL amyloidosis comprises chemotherapy directed towards the underlying clonal plasma cell disease, with the objective of reducing production of amyloidogenic monoclonal immunoglobulin light chains. Combined oral melphalan and prednisolone is of proven but very modest benefit in AL amyloidosis[10] and more dose-intensive regimens are now usually pursued. Recent British guidelines favour intermediate-dose chemotherapies, such as vincristine, adriamycin and dexamethasone (VAD) or monthly intravenous melphalan with dexamethasone.[11]

Chemotherapy that reduces circulating free immunoglobulin light chain (FLC) concentrations can greatly enhance survival.[12,13] In a recent study, the five-year survival of AL patients was 88% in those with more than a 50% reduction in their FLC, compared to 39% in those whose FLC did not fall by half ($p<0.0001$).[13]

High-dose chemotherapy and autologous stem cell transplantation

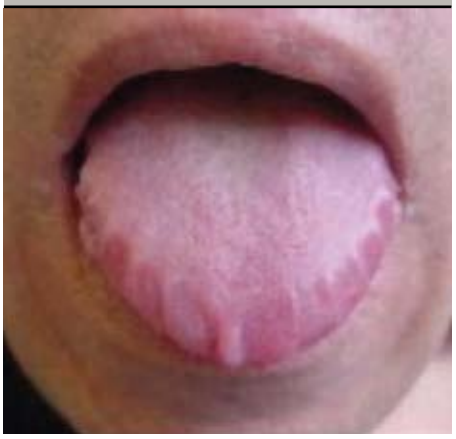
High-dose chemotherapy with melphalan supported by autologous stem cell transplantation has been used increasingly in AL amyloidosis.[14] Response rates in terms of clonal disease remission are encouraging with centres reporting a complete haematologic response in as many as 40% of eligible patients. However, mortality rates are appreciable with experienced centres reporting values between 13% and 20%.[15,16] The overall impression is that patients with advanced disease, and particularly those with cardiac decompensation, tolerate this therapy poorly.

Additional and alternative therapies

Following success with its use in myeloma, the drug thalidomide has been tried both alone and in combination with chemotherapy,[17] although high-dose thalidomide is not well tolerated by subjects with AL amyloid.[18] Recently, the combination of thalidomide and intermediate-dose dexamethasone has been shown to be effective in a proportion of patients (48%) who are refractory to therapy. Again, as with high-dose thalidomide, treatment-related toxicity was frequent (65%).[19]

The tumour necrosis factor inhibitor etanercept has been trialled in a small cohort with advanced AL amyloidosis, with 50% of patients appearing to benefit objectively and 88% reporting subjective benefit in symptoms.[20]

Figure 3. Macroglossia showing teeth indentations in a patient with AL amyloid disease



As yet there is no specific treatment for amyloid that has been proven to promote its regression, though many candidate drugs have been tested over the years. Recent studies of a doxorubicin derivative (I-DOX), a cytotoxic anthracyclin, suggested promise,[21] but subsequent data were inconclusive,[22,23] and it is notably toxic.

Heart transplantation for AL amyloid heart disease

The UK experience was reported in 2004 for a total of 24 patients (17 AL and seven non-AL amyloid).[24] Regardless of the use of adjunctive chemotherapy, the five-year survival after heart transplantation was generally poorer for AL (20% at five years), but similar for non-AL amyloidosis (64% at five years), than following heart transplantation for other indications. Progression of the systemic disease contributed to the increased mortality. Experience from the United States is similarly disappointing in AL patients undergoing heart transplantation.[25]

The non-AL amyloidoses

Within the non-AL categories of amyloid, of the 75 mutations known to express a clinical phenotype, around 44 (59%) involve the heart with a cardiomyopathy. Some deposited proteins cause cardiac compromise on a par with AL amyloid. The true frequencies of these individual types of amyloid are very difficult to estimate, largely due to the fact that many patients remain undiagnosed or misdiagnosed, and it may be of relatively late onset in life.

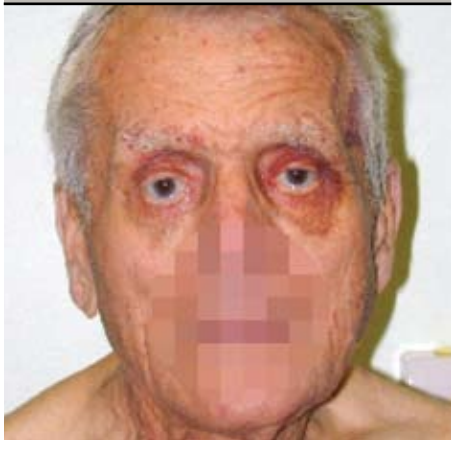
In the non-AL types, inquiry about a family history, with particular attention to any neurological diseases, is important. The caveat to this is that penetrance of these autosomal dominant genes is not always 100%. Patients with many of the non-AL forms of inherited amyloidosis frequently present with a progressive sensorimotor neuropathy. Macroglossia is not a feature, although carpal tunnel syndrome may be an early indicator of the disease. Clinical features will depend on the protein sub-unit, the actual mutation and, frequently, the kindred within which the mutation is 'embedded'.

As in AL amyloid heart disease, a restrictive cardiomyopathy is often the ultimate cause of death (**figure 1**), and fatal cardiac arrhythmias are also a feature. Echocardiographically, a hereditary form of amyloidosis may be indistinguishable from AL amyloidosis.[26]

Hereditary amyloidosis

Autosomal dominant hereditary amyloid is probably the second most common type of amyloid encountered by cardiologists, though the familial aetiology is often not obvious. Usually these forms are associated with a mutation of the plasma protein transthyretin (TTR). Around 100 different amyloidogenic mis-sense point mutations of TTR have already been described. One such is particularly common in patients of black African origin. Heart involvement is not uncommon and can also occur with variants of hereditary fibrinogen and apolipoprotein-AI amyloid.

Figure 4. Peri-orbital haemorrhage (raccoon or panda eyes) occurring spontaneously is one of the classic stigmata of AL amyloidosis



Management of hereditary amyloidosis

In patients with hereditary amyloidosis, where the amyloidogenic protein is predominantly produced by the liver (TTR and fibrinogen mutations), orthotopic liver transplantation provides a treatment by removing the source of the mutant protein.[27,28] Initial hopes for liver transplantation as a cure have been tempered by reports of progression of amyloid deposition in native hearts and donor hearts simultaneously transplanted with livers.[29] It appears that wild-type TTR may continue the amyloid deposition, after liver transplantation has eliminated the TTR variant that initiated the amyloidogenic process.[30]

Experience with apolipoprotein AI amyloidosis and cardiac involvement is less well described. Patients with mutations of the apoprotein AI molecule, may require combined heart and kidney transplantation, because of a predilection for apoprotein AI amyloid deposition in the kidneys with resultant renal failure.

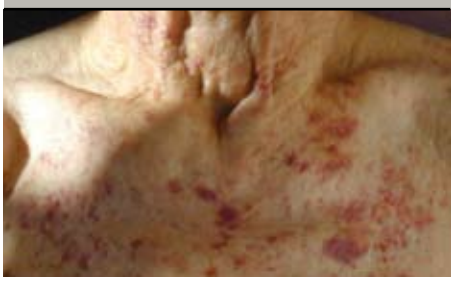
Additional and alternative therapies

A drug is already being tested in patients that targets SAP with the goal of eliminating SAP from amyloid deposits, in the hope that this may reduce amyloid deposition and/or accelerate amyloid clearance. Small molecule ligands that stabilise the native tetrameric structure of TTR and prevent its fibrillogenesis are being actively investigated for prophylaxis and therapy in TTR amyloidosis. Diflusinal has recently been found to stabilise the structure of TTR. This action reduces tetramer dissociation and subsequent monomer misfolding and aggregation into amyloid. A trial of its clinical efficacy is in progress and several similar, and possibly more potent, agents are in development.

Senile systemic amyloidosis

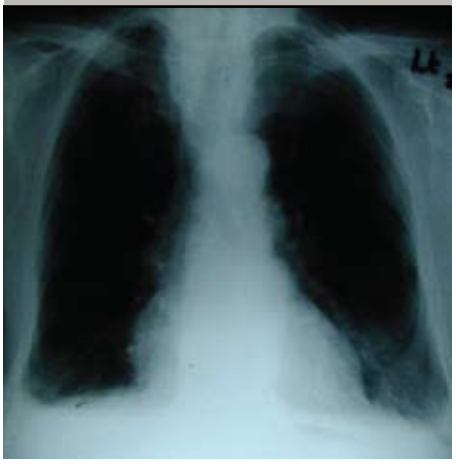
Normal wild-type TTR is in itself weakly amyloidogenic and wild-type TTR amyloid deposition is remarkably common in individuals over 70–80 years of age. Unlike genetically variant forms, wild-type TTR amyloid deposits are largely confined to the heart.[31] Cardiac deposition of wild-type TTR may sometimes be massive, resulting in severe heart failure.[32] The echocardiographic

Figure 5. Petechiae over the front of the chest in an elderly patient with advanced AL amyloidosis



appearance is typical of other forms of amyloidosis, but there is no neuropathy or other major extracardiac involvement. It is almost exclusively a disease of elderly men. A recent report comparing patients with AL and senile amyloid heart involvement found that patients with senile cardiac amyloid had ventricular walls even thicker than those with AL.[33] However, despite thicker walls and being older, the senile amyloid patients had less severe heart failure and a much longer median survival (75 *vs.* 11 months). Treatment is directed at symptom relief with conventional heart failure therapies. Heart transplantation is a reasonable consideration in patients with advanced SSA heart involvement, but only if they present at a young enough age. Despite the terminology ('senile' amyloid), occasionally patients are under 60 years of age and eligible for transplantation.[24]

Figure 6. A chest radiograph of a patient with severe AL amyloid heart disease on echocardiography. The cardiothoracic ratio is only mildly enlarged. Bilateral small pleural effusions are seen



Secondary amyloidosis

AA amyloidosis is a rare complication of chronic inflammatory disorders. The fibrils are derived from the acute phase reactant serum amyloid A protein. Although cardiac deposits are often present at histology, echocardiographic abnormalities and clinical symptoms of cardiac AA amyloidosis are extremely rare, occurring in about 2% of cases. The prognosis is substantially better than in cases of AL amyloid.[34] Treatment involves suppressing the underlying inflammatory disease.

Isolated atrial amyloid

Atrial natriuretic peptide (ANP) is synthesised locally by atrial myocytes,[35] and can be deposited locally within the atria as amyloid. It may be important in the development of atrial conduction abnormalities and atrial fibrillation. IAA is a disease of the elderly, with a female preponderance that contrasts with an almost male exclusivity of senile TTR amyloid.[33] The incidence of IAA in elderly hearts is high, with one autopsy study describing IAA in 91 of 100 hearts.[36] No specific therapy exists to treat IAA and management centres on controlling rhythm disturbance.

Conclusion

Late diagnosis remains one of the main hindrances to the management of amyloidosis. Once identified, it is vital to precisely determine the type of amyloid as both the prognosis and treatment differ very considerably among the types.

The goal remains, to prevent production and deposition of constituent monomer building blocks, to destabilise assembled fibrils and solubilise the amyloid deposits into non-pathogenic constituents

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Conflict of interest

SWD has received payments from Pfizer for data analysis on drug development in the treatment of amyloid.

Key messages

Amyloid disease

- The National Amyloid Centre for the UK is located at the Royal Free Hospital and provides a diagnostic and management advisory service for the NHS
- The diagnosis is frequently missed and, when detected, the type of amyloid incorrectly assigned
- A signatory cardiac feature is a thick-walled heart in combination with a low-voltage electrocardiogram
- The amyloidoses are systemic diseases that may mimic many other clinical conditions
- The clinical importance of senile systemic amyloid (SSA) may be underestimated
- Always ask about a family history, particularly of neurological disease

AL amyloid

- Classic stigmata of AL amyloid include macroglossia and 'raccoon eyes'
- Consider the diagnosis in patients with nephrotic range proteinuria and heart failure
- Consider occult involvement of other vital organs when haemodynamic status is impaired, i.e. thyroid and adrenal glands
- Advanced cardiac disease at presentation carries a very poor prognosis
- Isolated heart involvement is extremely unusual in this systemic disease
- Sudden death is common

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